Uses of Monoclonal Antibody (mAb) Therapy for Covid-19

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Disclosure Statement

- Dr. Brooke Rossheim has no financial or other conflicts of interest to disclose regarding this talk

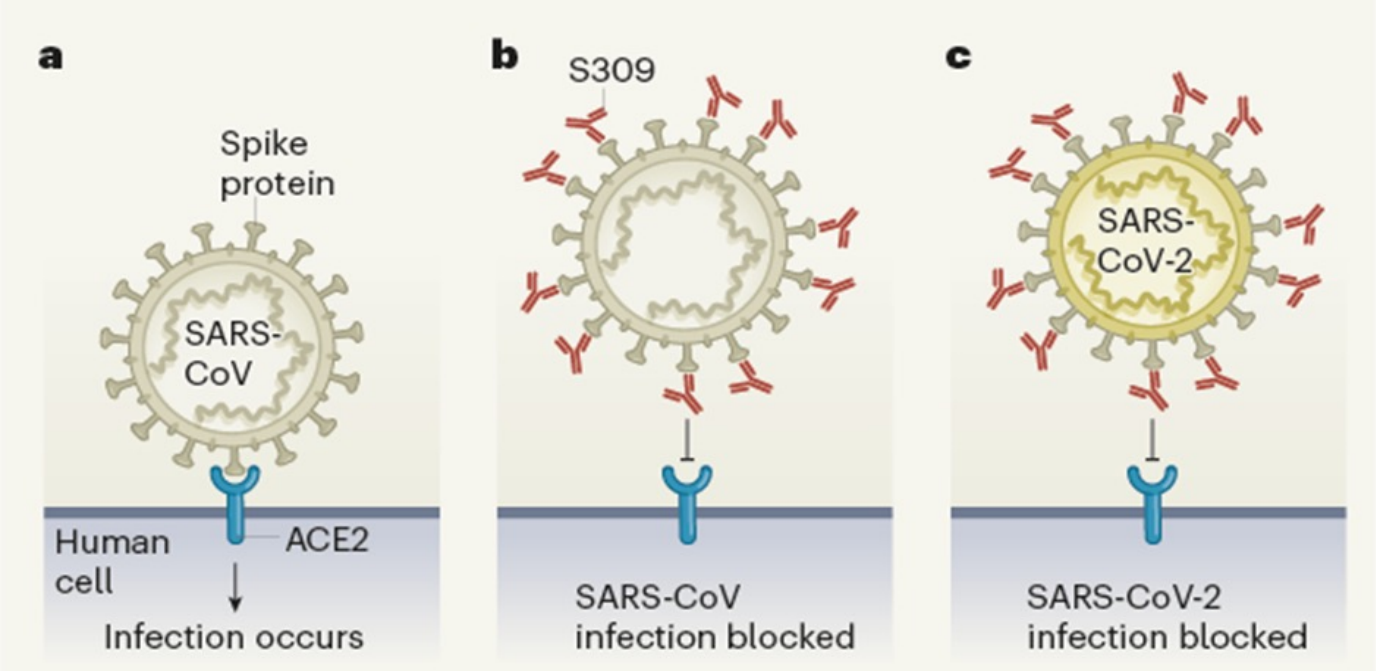
Monoclonal Antibodies (mAbs) with FDA Emergency Use Authorizations (EUAs) for **outpatient** Covid-19 Use

- **Casirivimab** (REGN10933) and **Imdevimab** (REGN10987) = **REGEN-COV** (Regeneron)
  - ***Of note: can be given by IV infusion OR 4 subcutaneous injections of 2.5 mL each***

- **Sotrovimab** (VIR-7831; GlaxoSmithKline/Vir Biotechnology)
  - Received FDA EUA on May 26, 2021

- "**Bam/Ete**" = **Bamlanivimab** (also known as LY-CoV555 or LY3819253) in combination with **Etesevimab** (also known as LY-CoV016 or JS016 or LY3832479) – both Eli Lilly drugs
  - **On June 25, 2021, "Bam/Ete" distribution put on hold by HHS, and FDA recommended that alternate mAbs be used for outpatient Covid-19 treatment because of an increased frequency of Beta and Gamma variants of SARS-CoV-2 which this drug was not felt to be effective against**
  - **On 9/2/2021, all restrictions lifted on Bam/Ete because the drug has activity against delta, and delta is by far the primary variant in the U.S.**

Monoclonal Antibody Mechanism of Action



Monoclonal antibodies (mAbs) directly neutralize SARS-CoV-2 virus and are intended to **prevent progression of disease.**

May be referred to as “blocking antibodies”

FDA EUA Indication #1 for outpatient mAb therapy

1. **TREATMENT of patients with mild to moderate Covid-19:**
   - **REGEN-COV (Regeneron), or**
   - **Sotrovimab (GSK), or**
   - **Bam / Ete (Lilly)**

- Regarding REGEN-COV, EUA package insert notes that “for treatment, IV infusion is strongly recommended. Subcutaneous injection is an alternative route of administration when IV infusion is not feasible and would lead to delay in treatment.”

FDA website with EUAs for Covid-19 drugs

Date of First EUA Issuance	Most Recent Letter of Authorization (PDF)	Authorized Use [1]	Fact Sheets and Manufacturer Instructions/ Package Insert (PDF)
11/21/2020	REGEN-COV (Casirivimab and Imdevimab) (506KB) (Reissued February 3, 2021, February 25, 2021, June 3, 2021, July 30, 2021 and September 9, 2021)	Casirivimab and imdevimab to be administered together for the treatment of mild to moderate COVID-19 in adults and pediatric patients (12 years of age and older weighing at least 40 kg) with positive results of direct SARS-CoV-2 viral testing, and who are at high risk for progression to severe COVID-19, including hospitalization or death.	Healthcare Providers (737KB) (updated September 9, 2021) Patients, Parents, and Caregivers (147KB) (updated July 30, 2021) • Spanish (247KB) Dear Healthcare Provider Letter (620KB) (updated September 9, 2021) Statement on Post-Exposure Prophylaxis (July 30, 2021) Frequently Asked Questions on the Emergency Use Authorization of REGEN-COV (Casirivimab and Imdevimab) (311KB) (updated July 30, 2021) CDER Scientific Review Documents Supporting EUA Quick Reference Guide for Co-Packaged REGEN-COV (150KB) (September 9, 2021

EUA for Treatment of Patients with Mild to Moderate COVID-19

- Casirivimab and imdevimab (REGEN-COV)
- Sotrovimab (GSK/Vir Biotech)
- Bamlanivimab and etesevimab (Lilly)*

1. Positive viral SARS-CoV-2 test (e.g., PCR or antigen test). Point-of-care test is fine.
2. Give medication as soon as possible after positive test. Must be given within 10 days of symptom onset. Pt cannot be hospitalized because of COVID-19.
3. Patient ≥ 12 years, weighs at least 40 kg; at high risk for progression to severe COVID-19. *As of 12/3/21, Bam/Ete can be used regardless of age.
4. Healthcare provider reviews EUA fact sheet; patient/caregiver provided with EUA fact sheet.
5. Administered in a setting where HCPs have direct access to medications to manage severe allergic reaction and activate EMS

EUA criteria for high-risk of progression to severe COVID-19

The following medical conditions or other factors may place adults and pediatric patients (age 12-17 years and weighing at least 40 kg) at higher risk for progression to severe COVID-19:

- Older age (for example, age ≥65 years of age)
- **Obesity or being overweight (for example, BMI >25 kg/m, or if age 12-17, have BMI ≥85th percentile for their age and gender based on CDC growth charts, www.cdc.gov/growthcharts/clinical_charts.htm)**
- Pregnancy
- Chronic kidney disease
- Diabetes
- Immunosuppressive disease or immunosuppressive treatment
- Cardiovascular disease (including congenital heart disease) or hypertension
- Chronic lung diseases (for example, chronic obstructive pulmonary disease, asthma [moderate-to-severe], interstitial lung disease, cystic fibrosis and pulmonary hypertension)
- Sickle cell disease
- Neurodevelopmental disorders (for example, cerebral palsy) or other conditions that confer medical complexity (for example, genetic or metabolic syndromes and severe congenital anomalies)
- Having a medical-related technological dependence (for example, tracheostomy, gastrostomy, or positive pressure ventilation (not related to COVID 19)

- For more info about high-risk patients, see CDC website **Underlying Medical Conditions Associated with High Risk for Severe COVID-19: Information for Healthcare Providers**

FDA EUA Indication #2 for outpatient mAb use

2. POSTEXPOSURE PROPHYLAXIS against COVID-19:

- **REGEN-COV (can be given IV or SC – no preference of one over the other), or**
- **Bam/Ete* – only by IV infusion**

Eligibility

- ***Patients 12 years of age and older*** who are at ***high risk for progression to severe COVID-19, AND***
- ***Not fully vaccinated or who are not expected to mount an adequate immune response*** to complete SARS-CoV-2 vaccination (for example, individuals who are immunosuppressed due to illness, medication, etc.) **AND**
  - Have been exposed to an individual with Covid-19 consistent with close contact criteria per CDC, **OR**
  - Who are at high risk of exposure to an individual with Covid-19 because of COVID-19 infection in other individuals in the same setting (for example, nursing homes or prisons)

* As of 12/3/2021, Bam/Ete can be used regardless of patient age

Monoclonal Ab Treatment Data

- REGN-COV 2067 Phase 3 Trial
  - Randomized, placebo-controlled trial
  - Casirivimab/imdevimab (REGEN-COV) 1200 mg (n=736) vs. placebo (n=748)
  - Meds given by IV infusion
  - **Results**: Outcome = Covid-19 related hospitalization or death
  - 1% in REGEN-COV 1200 mg group vs. 3.2% with placebo – highly statistically significant difference – a 70% risk reduction

- Phase 3 "BLAZE-1" study published as a press release from Eli Lilly – see https://investor.lilly.com/news-releases/news-release-details/lillys-bamlanivimab-and-etesevimab-together-reduced

  - 769 high-risk patients, aged 12 and older with mild to moderate Covid-19
  - 511 pts received bam/ete; 258 received placebo
  - Outcome studied = Covid-19-related hospitalizations and deaths
  - 4 events in the bam/ete group vs. 15 in placebo group – an 87% risk reduction that was highly statistically significant

Monoclonal Ab Treatment Data (continued)

- Sotrovimab treatment study - double-blind trial (COMET-ICE) summarized in FDA Fact Sheet on sotrovimab
  - 583 adult outpatients with mild-moderate Covid-19
  - Sotrovimab IV x 1 dose vs. placebo
  - Results: Primary endpoint = progression of Covid-19 (hospitalization > 24 hours or death from any cause) occurred in 1% in sotrovimab group vs. 7% with placebo
  - 86% risk reduction for primary endpoint – highly statistically significant

Monoclonal Ab Postexposure Prophylaxis Data

REGEN-COV postexposure prophylaxis study:

O'Brien MP, Forleo-Neto E et al. Subcutaneous REGEN-COV Antibody Combination to Prevent Covid-19. NEJM. Accessed www.nejm.org/doi/full/10.1056/NEJMoa2109682 on 8/12/2021.

- 1505 participants receive either subcutaneous REGEN-COV 1200 mg vs. placebo
- Participants randomized to REGEN-COV vs. placebo within 96 hours after collection of the index patient's positive SARS-CoV-2 diagnostic test, and persons with previous SARS-CoV-2 infection were excluded
- Primary efficacy end point = percentage of participants in whom symptomatic, RT-qPCR–confirmed SARS-CoV-2 infection developed during 28-day assessment period
- Results: 1.5% of participants in REGEN-COV group met the primary endpoint vs. 7.8% in the placebo group
- 81% risk reduction; $p<0.001$

Recent mAb Developments

- **September 9, 2021**: 9th Amendment to HHS PREP Act Declaration is released
  - **expands the scope of authority for licensed pharmacists to order and administer select COVID-19 therapeutics to populations authorized by the FDA, and for pharmacy technicians and pharmacy interns to administer COVID-19 therapeutics**
  - **Licensed pharmacist can order SC, IM, or oral Covid-19 therapeutic in accordance with FDA EUA**
  - Currently, this would only apply to SC administration of REGEN-COV

Recent mAb Developments (continued)

- **September 13, 2021**: HHS notifies state and territorial health depts. and mAb administration sites that ALL orders will go to state/territorial health dept. Each state/territory will receive a weekly allocation of mAb doses from HHS. Health dept will determine which site(s) gets mAb therapy and how many doses. See notice here.

- Rules regarding program:
  - Once weekly HHS allocation - based on state's mAb usage and Covid-19 cases
  - States/territories cannot exceed weekly allocation – can't ask for extra doses
  - Don't stockpile mAbs – order one week at a time
  - mAbs that are NOT used one week do NOT carry over to the next week
  - At least 70% of mAbs must be used during week, o/w allocation may be reduced next week
  - mAb administration sites must report usage to HHS
  - New sites must register with AmerisourceBergen (distributor) and HHS before they can receive mAbs

- VDH already in contact with Virginia Disaster Medical Advisory Committee (VDMAC) regarding approach if demand for mAbs far exceeds supply

Recent mAb Developments (continued)

- Other than first week, Virginia's allocation of mAbs has been very good:
  - First week (9/13/2021): 1530 doses of Bam/Ete and REGEN-COV
  - Second week (9/20/2021): ~3900 doses of Bam/Ete and REGEN-COV
  - Third week (9/27/2021): 4476 doses of REGEN-COV and Bam/Ete
  - Fourth week (10/4/2021): 4476 doses of REGEN-COV and Bam/Ete.
  - Fifth week ("Cycle 5"): 4046 doses of REGEN-COV, Bam/Ete, and sotrovimab (first week that sotrovimab received)
  - Sixth week ("Cycle 6"): 3676 doses of monoclonal antibodies
  - Seventh week ("Cycle 7"): 3668 doses of monoclonal antibodies
  - Eighth week ("Cycle 8"): 2536 doses of monoclonal antibodies
  - Ninth week ("Cycle 9"): 1828 doses of monoclonal antibodies
  - Tenth week ("Cycle 10"): 3126 doses of monoclonal antibodies for 2 weeks
  - "Cycle 11": 3126 doses of monoclonal antibodies for 2 weeks ending 12/10/21

Monoclonal Antibody Therapy "Nuts & Bolts"

- **VDH COVID-19 Monoclonal Antibody Webpage** (www.vdh.virginia.gov/mabs)
  - Bamlanivimab/Etesevimab (Lilly) Fact Sheets: Physician Patient
  - Casirivimab/Imdevimab (REGEN-COV) Fact Sheets: Physician Patient
  - Sotrovimab (GSK/Vir Biotechnology) Fact Sheets: Physician Patient
  - mAb Infusion Sites in Virginia (Excel spreadsheet) – also, see National Infusion Center Association (NICA) Infusion Center Locator (https://locator.infusioncenter.org/)
  - Reimbursement & Coding
  - Bam/Ete and REGEN-COV ordering – now through VDH
  - Sotrovimab ordering – now through VDH
  - Training & Education
  - Infusion Toolkit
  - Additional Resources

Cost and availability of monoclonal antibody products

- Department of Health and Human Services (HHS) has purchased Bam/Ete (Lilly), REGEN-COV, and most recently sotrovimab – these drugs are available at no cost to monoclonal Ab administration site

- **Patients are not charged for the drug, but they may be charged for their clinic visit/infusion services**

Medicare Payment for COVID-19 Monoclonal Ab Infusion

In order to ensure immediate access during the COVID-19 PHE, Medicare will reimburse for these infusions in accordance with 3713 of the CARES Act

- **Payment for infusion:** Medicare reimbursement ranges from approximately $450. to $750. for subcutaneous or intravenous infusion effective 5/26/21 (Medicare national average)
- **Payment for product:** No payment for COVID-19 monoclonal antibody (mAb) products that providers receive for free. If providers begin to purchase these mAb products, CMS anticipates setting the payment rate in the same way as the payment rate for COVID-19 vaccines

Providers can bill for COVID-19 mAb infusion on a single claim for or submit claims on a roster bill, in accordance with the EUA for each product

- The EUA for COVID-19 mAb treatments contain specific requirements for administration that are more complex than for other services that are billed using roster billing. Providers are expected to maintain medical documentation that supports the medical necessity (i.e., EUAs are met, provider names, etc.)
- Providers should not include the COVID-19 mAb codes on the claim when the product is provided for free
- For most up-to-date list of billing codes, payment allowances and effective dates

Provider Payment Key Facts

- CMS will exercise enforcement discretion to allow Medicare-enrolled immunizers working within their scope of practice and subject to applicable state laws to bill directly and receive direct reimbursement for administering mAb treatments to Medicare Part A Skilled Nursing Facility residents

- Medicare will not pay the provider for mAb products when they are given to the provider free of charge.

- For patients who have no health insurance, COVID-19 services can be provided and the medical provider / organization can submit claims to the U.S. Health Resources and Services Administration (HRSA) COVID-19 Uninsured Program. This program covers just about all COVID-19-related services. See https://www.hrsa.gov/coviduninsuredclaim for more information
  - Patient must not have any health insurance
  - COVID-19 MUST be the primary diagnosis

General mAb Resources

- Monoclonal antibody therapies available under an EUA must be used in accordance with the terms and conditions for the respective authorization, including the authorized labeling. The Letters of Authorization may be accessed at: https://www.fda.gov/emergency-preparedness-and-response/mcm-legal-regulatory-and-policy-framework/emergency-use-authorization#coviddrugs

- https://www.seektreatmentnow.com/ = Regeneron Pharmaceuticals, Inc. website

- https://www.lilly.com/news/stories/2021-coronavirus-covid19-global-response = Eli Lilly Covid-19 response website

- www.sotrovimab.com = GlaxoSmithKline webpage with sotrovimab resources

- https://combatcovid.hhs.gov/i-have-covid-19-now/monoclonal-antibodies-high-risk-covid-19-positive-patients = Excellent website from Department of Health and Human Services about monoclonal antibody therapy

- VDH COVID-19 Outpatient Monoclonal Therapy Resource Center = www.vdh.virginia.gov/mabs - has information at the top of page about becoming a mAbs administration site

For questions or more information, please contact:

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Appendix

- Centers for Medicare & Medicaid Services (CMS) Payment Allowances for Outpatient Monoclonal Antibodies

Payment Allowances and Effective Dates for COVID-19 Monoclonal Antibodies and their Administration During the Public Health Emergency:

HCPCS Code	HCPCS Short Descriptor	Labeler Name	Vaccine/Procedure Name	National Payment Allowance Effective for Claims with DOS on or after 05/6/2021	National Payment Allowance Effective for Claims with DOS through 05/5/2021	Effective Dates
M0245	Bamlan and etesev infusion	Eli Lilly	intravenous infusion, bamlanivimab and etesevimab, includes infusion and post administration monitoring	$450.00[3]	$309.600[3]	02/09/2021 – TBD
M0246	Bamlan and etesev infus home	Eli Lilly	Intravenous infusion, bamlanivimab and etesevimab, includes infusion and post administration monitoring in the home or residence; this includes a beneficiary's home that has been made provider-based to the hospital during the covid-19 public health emergency	$750.00[3]	Code not active during this time period	05/06/2021 – TBD

Source: https://www.cms.gov/medicare/medicare-part-b-drug-average-sales-price/covid-19-vaccines-and-monoclonal-antibodies

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M0243	Casirivi and imdevi inj	Regeneron	IV or subcuteaneous injection, casirivimab and imdevimab includes infusion or injection, and post administration monitoring	$450.00[3]	$309.600[3]	11/21/2020 - TBD
M0244	Casirivi and imdevi inj hm	Regeneron	IV or subcuteaneous injection, casirivimab and imdevimab includes infusion or injection, and post administration monitoring in the home/ residence; this includes a beneficiary's home that has been made provider-based to the hospital during the covid-19 public health emergency	$750.00[3]	Code not active during this time period	05/06/2021 - TBD

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M0247	Sotrovimab infusion	GSK	IV infusion, sotrovimab, includes infusion and post administration monitoring	$450.00[3]	Code not active during this time period	05/26/2021 – TBD
M0248	Sotrovimab inf, home admin	GSK	IV infusion, sotrovimab, includes infusion and post administration monitoring in the home or residence; this includes a beneficiary's home that has been made provider-based to the hospital during the public health emergency	$750.00[3]	Code not active during this time period	05/26/2021 – TBD